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EXAMINER
MYERS, CARLA J

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/928,102	Applicant(s) PERLS ET AL.	
	Examiner Carla Myers	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

1. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a longevity-associated locus or marker and a locus or marker associated with resistance to age-related disease wherein the locus or marker comprises a region of chromosome 4 having linkage to the marker D4S1564, or contained within a 20 cM region surrounding said D4S1564 marker. The specification provides the results of a study of 308 individuals belonging to 137 families in which at least one sibling was 98 years old and a second sibling was at least 95 years old (female) or 91 years old (male). LOD score analysis (see Table 1) identified linkage between longevity and the genetic markers D4S1564 (MLS=3.65), D4S411 (MLS=3.07), D4S1572 (MLS=3.07), D4S2986 (MLS=2.78), and D4S406 (MLS=2.55). The specification (page 7) states that "A dropoff of 1.5 in the MLS score on either side of the peak MLS defines the area in which we can be 95% confident the gene resides. A dropoff in the MLS of 2 on either side of the peak is observed in a 20-cM region encompassed by D4S414 and D4S1611". It is generally accepted in the art that LOD scores of 3.0 and above are indicative of linkage. Accordingly, while the D4S1564, D4S411, and D4S1572 genetic markers meet the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the genus of any genetic locus or genetic marker associated with longevity or resistance to age-related disease wherein the locus or marker comprises a region

linked to the D4S1654 marker or within 20 cM of the D4S1564 marker. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, while the specification has taught 3 genetic markers linked to longevity and the prior art of Weissenbach teaches the nucleotide sequence of these genetic markers, the specification has not disclosed genetic loci linked to longevity and age-related diseases. The broadest reasonable interpretation of the claims indicates

that the claims are also inclusive of genes and allelic variants of genes that are associated with longevity or resistance to age-related diseases. The specification has not identified or clearly defined any particular genes on chromosome 4 in terms of structure (length, nucleotide sequence, start and stop positions, intron and exon positions etc) that are linked to longevity or resistance to age-related disease, nor has the specification taught a specific position on chromosome 4 on which a gene associated with longevity or resistance to age-related disease resides. The specification has also not identified any allelic variants of a gene that might be associated with longevity or age-related disease. Further, the teachings in the specification of linkage between the D4S1564, D4S411, and D4S1572 genetic markers and longevity is not sufficient to support the allegation that these markers are also associated with resistance to age-related disease. The specification (page 5) defines age-related diseases as including, but not limited to, heart disease, cardiovascular disease, stroke, Alzheimer's disease, cancer, and ocular disease. There is no specific showing in the specification to support the characterization of the D4S1564, D4S411, D4S1572, D4S2986 and D4S406 genetic markers as being linked to any of these specific age-related diseases. Accordingly, the specification has adequately defined 3 genetic markers associated with longevity, namely D4S1564, D4S411, and D4S1572 in terms of their structural properties. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., in terms of a specific functional activity, in terms of a specific protein encoded by a nucleic acid, etc). In the instant case, no such identifying characteristics have been provided for any additional genetic

loci. While genetic markers within 20 cM of D4S1564 are known in the art, the teachings in the specification (page 7) indicate that markers at a distance of 20 cM surrounding D4S1564 are not sufficiently linked to longevity. For example, in the study presented in the specification, the marker D4S414 had a MLS of 1.53 and the marker D4S1611 had a MLS of 1.70. While one could determine the sequence of the 20 cM region surrounding the D4S1564 marker, knowledge of the sequence alone does not identify and adequately characterize specific genetic loci and genetic markers associated with longevity or resistance to age-related diseases. Therefore, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed to include any genetic marker or genetic locus on chromosome 4 linked to the D4S1564 marker or within 20 cM of the D4S1564 marker wherein the genetic marker or genetic locus is associated with longevity or resistance to age-related diseases. Thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

2. Claims 7-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining if an individual has an increased propensity for longevity, wherein the method comprises obtaining DNA from a first individual and DNA from a second individual who is at least 98 years of age; amplifying DNA from said first and second individuals to obtain an amplification product wherein the amplification product comprises the

D4S1564 marker of human chromosome 4 and the amplified product contains nucleotide sequences within a region flanked by the genetic markers D4S1564 and D4S1572; comparing the amplified DNA product from the first and second individual, wherein when the amplified DNA product of the first individual is identical to that of the second individual, the first individual is identified as having an increased propensity for longevity, does not reasonably provide enablement for methods for determining a propensity for age-related disorders; or methods for determining a propensity for longevity wherein the methods comprise detecting a polymorphic variant of the D4S1564 marker as indicative of a propensity for longevity; or methods for determining a propensity for longevity wherein the methods comprise detecting a polymorphic variant in a region of chromosome 4 that contains the D4S1564 marker. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 7-10 are drawn to methods for identifying an individual with a propensity for longevity (claims 7 and 8) or a propensity for age-related disease (claims 9 and 10), wherein the methods comprise detecting a polymorphic variant of the D4S1564 marker. Claims 11-14 are drawn to methods for determining a propensity for longevity (claims 11 and 12) or a propensity for age-related diseases (claims 13 and 14) wherein the methods comprise comparing a DNA fragment of chromosome 4 comprising the D4S1564 marker between a first individual and a second individual who is at least 98 years of age and detecting the presence of a polymorphic variant in the DNA fragment, particularly wherein the polymorphic variant is contained within an

approximately 20 cM region surrounding said D4S1564 marker, and determining that the first individual has a propensity for longevity if said polymorphic variant is detected in both the DNA from the first individual and second individual. The specification provides the results of a study of 308 individuals belonging to 137 families in which at least one sibling was 98 years old and a second sibling was at least 95 years old (female) or 91 years old (male). Table 1 of the specification provides information regarding the results of a LOD score analysis between longevity and the following genetic markers: D4S1564 (MLS=3.65), D4S411 (MLS=3.07), D4S1572 (MLS=3.07), D4S2986 (MLS=2.78), and D4S406 (MLS=2.55). The specification (page 7) states that "A dropoff of 1.5 in the MLS score on either side of the peak MLS defines the are in which we can be 95% confident the gene resides. A dropoff in the MLS of 2 on either side of the peak is observed in a 20-cM region encompassed by D4S414 and D4S1611". Further, it is generally accepted in the art that LOD scores of 3.0 and above are indicative of linkage. Accordingly, a comparison between a DNA fragment of a test individual and an individual at least 98 years of age wherein the DNA fragment consists of a nucleotide sequence within the region flanked by markers D4S1564 and D4S1572 would provide information regarding the inheritance of a genetic marker linked with longevity and could be used in a diagnostic method to predict the likelihood that an individual has an increased propensity for longevity. However, the specification has not identified any particular polymorphic variants of the D4S1564 marker or polymorphic variants within 20 cM of the D4S1564 marker which are correlated with longevity or age-related diseases and thereby has not sufficiently enabled methods for predicting

propensity for longevity or resistance to drug-related diseases by detecting such polymorphic variants. The identification of a specific polymorphic variant, whether it be a variant of a genetic marker or an allelic variant of a gene, can only be determined through extensive experimentation. Secondly, the teachings in the specification (page 7) indicate that markers at a distance of 20 cM surrounding D4S1564 are not sufficiently linked to longevity. For example, the marker D4S414 had a MLS of 1.53 and the marker D4S1611 had a MLS of 1.70. Accordingly, the specification has not enabled methods which detect polymorphic variants within an approximately 20 cM region surrounding the D4S1564 marker. Thirdly, the teachings in the specification of linkage between the D4S1564, D4S411, and D4S1572 genetic markers and longevity is not sufficient to support the allegation that these markers are also associated with resistance to age-related disease. The specification (page 5) defines age-related diseases as including, but not limited to, heart disease, cardiovascular disease, stroke, Alzheimer's disease, cancer, and ocular disease. There is no specific showing in the specification to support the characterization of the D4S1564, D4S411, D4S1572, D4S2986 and D4S406 genetic markers as being linked to any of these specific age-related diseases. While individuals who live to be 98 years old may have increased resistance to age-related diseases, there is no evidence that any particular marker or genetic locus on chromosome 4 is sufficiently linked to resistance to specific age-related diseases. Further, the specification has not taught any polymorphic variants correlated with a "propensity for age-related disease" and insufficient guidance is provided in the specification as to how to identify without undue experimentation specific markers, loci and allelic variants that are tightly

correlated with age-related diseases. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the state of the art of identifying polymorphic variants correlated with specific conditions, particularly conditions as complex and broad as longevity and resistance to age-related diseases, is highly unpredictable. Clearly, extensive experimentation would be required to identify a particular polymorphic variant that could be used to directly detect whether an individual has a propensity for longevity or resistance to age-related diseases. Insufficient guidance is provided in the specification as to how to predictably identify, without undue experimentation, a specific polymorphic variant associated with longevity within a 20 cM region surrounding the D4S1564 marker. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

3. Claims 1-4 and 7-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 are indefinite over the recitation of "having a linkage" because this language is vague and does not clearly set forth the relationship or degree of linkage between the D4S1564 marker and the genetic locus.

Claims 7-14 are indefinite because it is unclear as to whether the methods detect an allelic variant of the D4S1564 marker or whether the methods detect an allelic variant of a marker within 20 cM of the D4S1564 marker. Claims 7, 9, 11, and 13 include the steps of amplifying a region comprising the D4S1564 marker and detecting a polymorphic variant of the D4S1564 marker. Yet, claims 8, 10, 12 and 14 recite the limitation "wherein said polymorphic variant is contained within an approximately 20 cM region surrounding said D4S1564 marker". Accordingly, it is unclear as to what is intended to be encompassed by the polymorphic variant of the D4S1564 marker and it is unclear as to whether the claimed method is one for detecting variants of D4S1564 or detecting variants of markers within 20 cM of D4S1564.

Claims 9, 10, 13 and 14 are indefinite for failing to recite a final process step which agrees back with the preamble. The claims are drawn to methods for identifying propensity for age-related diseases. However, the final process step is one for determining whether a subject has a propensity for resistance to age-related diseases. Accordingly, it is unclear as to whether the claims are intended to be limited to methods for determining whether a subject has a

propensity for age-related diseases or one for determining if a subject has a resistance to age-related diseases.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Weissenbach (GenBank Accesion No's Z23817, Z16811, Z23876, Z53755, and Z16728).

Weissenbach teaches isolated nucleic acids consisting of the nucleotide sequence of the D4S1564 genetic marker (GenBank Accession No. Z23817), the D4S1572 genetic marker (GenBank Accession No. Z23876), the D4S2986 genetic marker (GenBank Accession No. Z53755), the D4S411 genetic marker (GenBank Accession No. Z16811), and the D4S406 genetic marker (GenBank Accession No. Z16728). In view of the breadth of the claims and in view of the teachings in the specification that it is a property of these genetic markers that they are associated with longevity and resistance to age-related diseases, the claims are anticipated by the nucleic acids of Weissenbach. To clarify, there is no requirement that Weissenbach teach that the genetic markers are associated with longevity or age-related diseases if, in fact, it is an inherent property of these genetic markers that they are associated with longevity or resistance to age-related diseases.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703) 605-1237.

Carla Myers
March 21, 2002

CARLA J. MYERS
PRIMARY EXAMINER